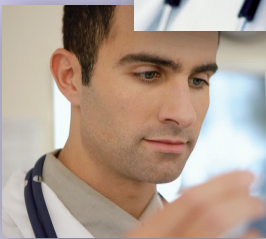
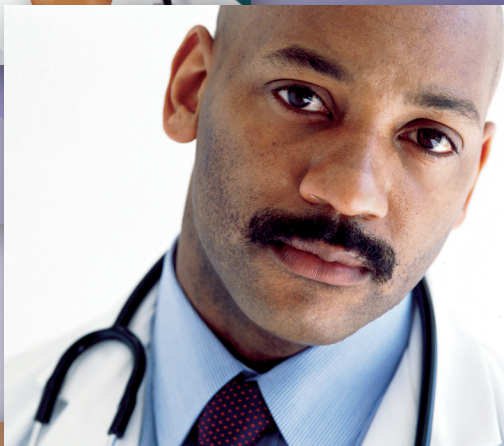


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SUPPLEMENT TO

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## PRACTICAL INSULIN STRATEGIES

### for type 2 diabetes in primary care

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- S25 Overcoming barriers to insulin replacement**  
Louis Kuritzky, MD

## Practical insulin strategies for type 2 diabetes in primary care

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**Dr Wright** has disclosed that he is on the advisory boards for Amylin Pharmaceuticals, Inc., Eli Lilly and Company, and Novo Nordisk Inc. and the speakers bureaus for Amylin Pharmaceuticals, Inc., and Eli Lilly and Company.

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### LEARNING OBJECTIVES

**After reading this supplement, the learner should be able to:**

- Explain the pharmacological basis for why current therapies are limited by their inability to control postprandial hyperglycemia.
- Apply steps to intensify insulin therapies to achieve improved glycemic control.
- Differentiate the clinical utility between long-acting, rapid-acting, and premixed insulin analogs.
- Restate the basal-bolus method of insulin administration.
- Explain the benefits and limitations of insulin analogs and premixed insulin analogs.

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# Overview of insulin replacement therapy

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### Disclosure

*Dr Wright has disclosed that he is on the advisory boards for Amylin Pharmaceuticals, Inc., Eli Lilly and Company, and Novo Nordisk Inc. and the speakers bureaus for Amylin Pharmaceuticals, Inc., and Eli Lilly and Company.*

## Importance of tight glycemic control for avoiding diabetes complications

Tight glycemic control is variously defined in clinical trials, but a glycosylated hemoglobin (A1C) value <7% is often set as a target for treatment, which is consistent with the American Diabetes Association (ADA) goals for patients with diabetes.<sup>1</sup> Although this goal may seem aggressive and is difficult for many patients to reach,<sup>2</sup> this value is substantially higher than that for patients without diabetes, whose A1C range is typically 4% to 6%.<sup>3</sup>

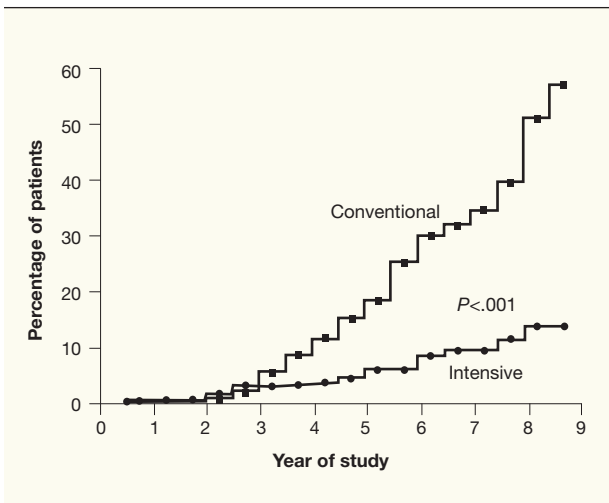
Achieving and maintaining tight glycemic control is important for avoiding, delaying, and/or decreasing the severity of long-term complications of diabetes. Long-standing diabetes can lead to irreversible organ damage, including cardiovascular disease, renal dysfunction, ocular impairment, and neuropathies that involve both sensory nerve fibers and the autonomic nervous system.<sup>4-8</sup> Results from landmark studies have demonstrated that tight glycemic control can decrease the risk for long-term complications in patients with type 1 or type 2 diabetes (FIGURES 1 AND 2).<sup>9-12</sup>

Although landmark studies have demonstrated important benefits of tight glycemic control in patients with type 1 or type 2 diabetes, initial results of recent studies challenged the knowledge that intensive therapy is invariably associated with lower A1C levels and better clinical outcomes for patients with type 2 diabetes. In a study of patients with type 2 diabetes following myocardial infarction (MI), the Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI 2) investigation<sup>13</sup> did not find any significant clinical or metabolic benefit of an acutely introduced, long-term insulin treatment program compared with conventional management. Similarly, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study<sup>14</sup> showed that, as compared with standard therapy, the use of intensive therapy to target an A1C level of <6% did not significantly reduce major cardiovascular events; rather, it increased mortality vs treatment aimed at an A1C goal of 7% to 7.9% in patients with high-risk diabetes. Two other recent studies, the Action in Diabetes and Vascular Disease (ADVANCE) study<sup>15</sup> and the Veterans Affairs Diabetes Trial (VADT)<sup>16</sup> have also indicated that intensive therapy (targeted at an A1C level ≤6.5% in ADVANCE and an A1C reduction of ≥1.5% in VADT) does not decrease cardiovascular mortality or events in patients with diabetes.

Experts in the care of patients with diabetes and cardiovascular disease

**FIGURE 1**

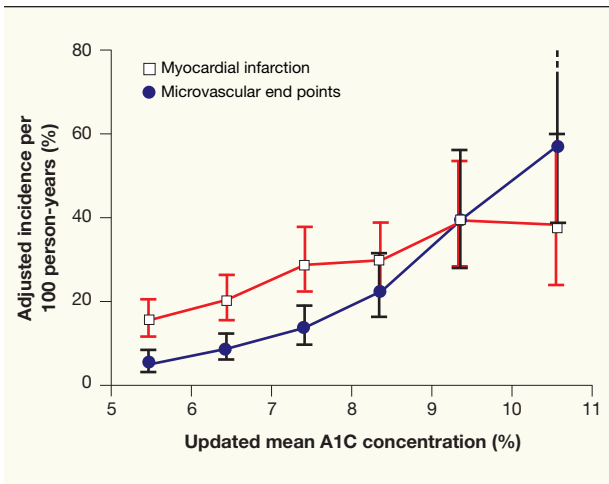
**Intensive glycaemic control and risk for microvascular complications**



Intensive glycaemic control decreased the risk for microvascular complications in patients with type 1 diabetes by 76%: cumulative incidence of retinopathy in the primary prevention cohort, assessed at years 3, 5, 7, and 9. Diabetes Control and Complications Trial Research Group. *N Engl J Med.* 1993;329:977-986. Copyright © 1993 Massachusetts Medical Society. All rights reserved.

**FIGURE 2**

**Intensive glycaemic control and risk for MI and microvascular complications**



A1C, glycosylated hemoglobin; MI, myocardial infarction. Intensive glycaemic control decreased the risk for macrovascular (myocardial infarction) and microvascular complications in white male patients aged 50 to 54 years at diagnosis with a mean duration of type 2 diabetes of 10 years. Each point shows the risk for myocardial infarction or microvascular end points as a function of A1C over the follow-up period. Bars represent 95% confidence intervals.

Reproduced from *British Medical Journal*; Stratton IM, Adler AI, Neil HA, et al; 321:405-412; Copyright © 2000 with permission from BMJ Publishing Group Ltd.

recently reevaluated the results from the ACCORD, ADVANCE, and VADT studies<sup>17</sup> and concluded that these studies did, in fact, indicate a benefit of tight glycaemic control in the primary prevention of cardiovascular events. This review also suggested multiple potential explanations for the increased mortality seen with tight glycaemic control in ACCORD vs other trials that did not have such a result. These explanations included the participation of patients with more advanced diabetes in the ACCORD trial, more rapid lowering of A1C levels in ACCORD vs the other studies, and a potentially increased risk for severe hypoglycemia that contributed to cardiovascular mortality.<sup>17</sup> This group also reaffirmed an A1C level <7% as the treatment goal for patients with diabetes.<sup>17</sup> However, less stringent goals might be suitable for patients with a history of severe hypoglycemia, limited life expectancy, or advanced diabetes complications, or for those with long-standing diabetes who have great difficulty achieving A1C levels <7% despite appropriate education and care.<sup>17</sup> Thus, treatment must be individualized on the basis of patient characteristics.

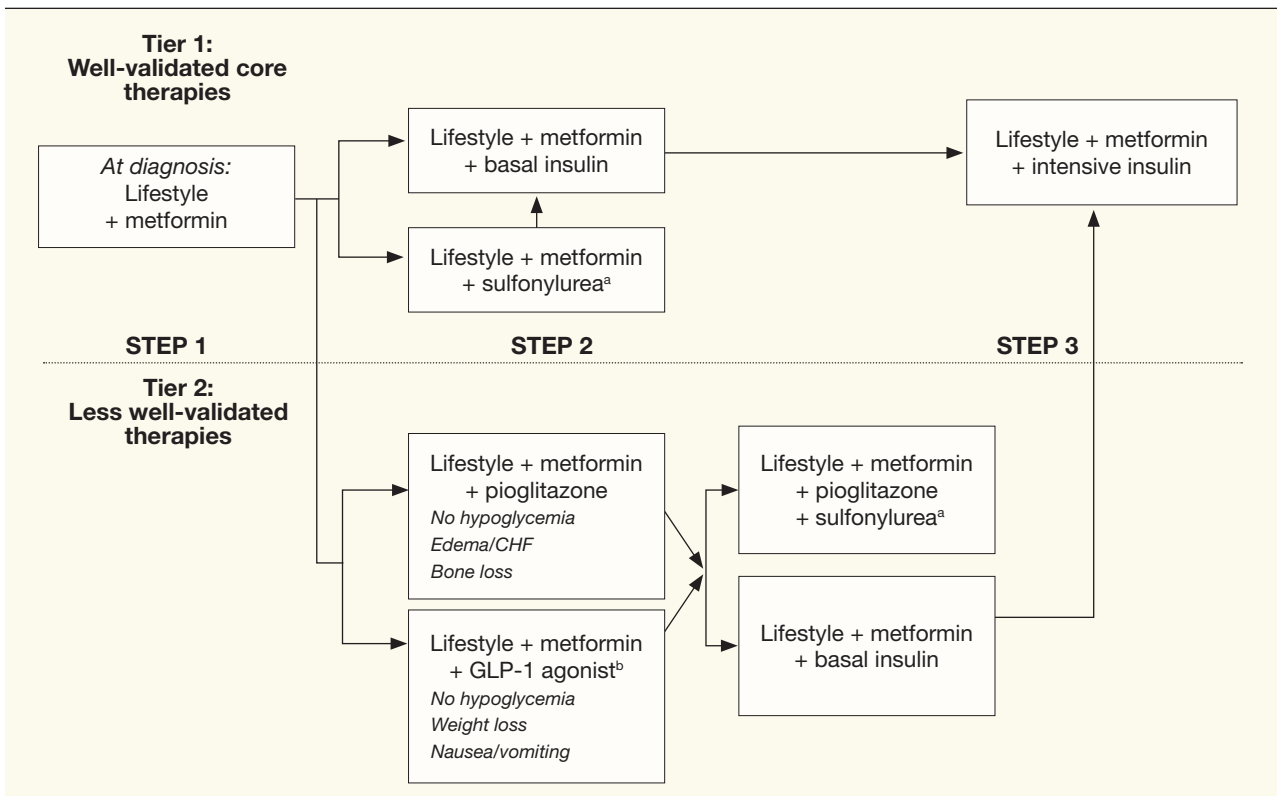
**The role of FPG and PPG in risk for complications**

Fasting plasma glucose (FPG) and postprandial glucose (PPG) both contribute to the risk for diabetes complications. PPG is believed to be a particularly important determinant of macrovascular risk in patients with diabetes. Results from the Honolulu Heart Study<sup>18</sup> showed that elevated 1-hour PPG is a strong predictor of risk for coronary heart disease mortality. Results from this study showed that men in the fourth quintile of postchallenge glucose (157-189 mg/dL) had twice the age-adjusted risk of fatal coronary heart disease vs those in the lowest quintile (40-114 mg/dL).

Assessment of the effects of therapy aimed at lowering PPG in the Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM) trial<sup>19</sup> indicated that treatment with acarbose (100 mg administered 3 times per day) was associated with decreased risk for silent MI vs placebo in patients with impaired glucose tolerance. This study also demonstrated that reducing PPG with acarbose was associated with a 49% relative risk reduction for the occurrence of cardiovascular events and a 91% decrease in the risk for MI. Treatment with acarbose also resulted in a 34% decline in the relative risk for development of

**FIGURE 3**

**The American Diabetes Association and European Association for the Study of Diabetes algorithm for the management of type 2 diabetes**



CHF, congestive heart failure; GLP, glucagon-like peptide.

<sup>a</sup> Sulfonylureas other than glybenclamide (glyburide) or chlorpropamide.

<sup>b</sup> Insufficient clinical use to be confident regarding safety.

Lifestyle intervention should be reinforced at every visit. Glycosylated hemoglobin (A1C) should be checked every 3 months until the A1C is <7% and at least every 6 months thereafter. Nathan DM, et al. Copyright © 2009 American Diabetes Association. From Diabetes Care, Vol. 32; 2009, 193-203. Reprinted with permission from The American Diabetes Association.

hypertension.<sup>20</sup> The Hyperglycemia and Its Effect After Acute Myocardial Infarction on Cardiovascular Outcomes in Patients With Type 2 Diabetes (HEART2D) study<sup>21</sup> determined the effects of PPG control on cardiovascular outcomes in patients who had had an MI within the 21 days before study enrollment. The trial compared two treatment strategies: (1) a postprandial strategy—premeal insulin lispro with basal insulin at bedtime if needed (neutral protamine Hagedorn [NPH] insulin), targeting 2-hour PPG  $\leq 7.5$  mmol/L ( $\leq 135$  mg/dL), and (2) a basal strategy—NPH insulin twice daily or insulin glargine once daily, or premixed human insulin (70% NPH/30% regular insulin) twice daily, targeting FPG and premeal blood glucose  $\leq 6.7$  mmol/L ( $\leq 120$  mg/dL). Both groups targeted an A1C level of <7%. Study results presented in 2008<sup>22</sup> indicated no significant between-group difference for

cardiovascular outcomes.

The Outcome Reduction With Initial Glargine Intervention (ORIGIN) trial<sup>23</sup> is being carried out to determine whether normoglycemia achieved with the long-acting insulin analog, insulin glargine, can reduce cardiovascular morbidity and/or mortality in people with impaired fasting glucose, impaired glucose tolerance, or early type 2 diabetes who are at high risk for vascular disease.

**ADA/EASD goals and treatment guidelines for type 2 diabetes**

As stated above, the ADA/EASD has established an A1C goal of <7.0% for adults with diabetes.<sup>24</sup> To achieve that goal, the initial recommended treatment for patients with type 2 diabetes is a combination of lifestyle chang-

es and metformin (FIGURE 3).<sup>24</sup> If an A1C level <7% is not achieved within 2 to 3 months, the recommended second step is the addition of either a basal insulin or a sulfonylurea to the treatment regimen. The third step for validated core therapies is to start or intensify insulin therapy.<sup>24</sup>

### Progressive nature of type 2 diabetes and loss of efficacy of oral antidiabetic drugs

In type 2 diabetes, there is not only impaired insulin secretion but also a progressive decline in  $\beta$ -cell function as well as chronic insulin resistance. Patients with this disease experience a reduction in islet and/or insulin-containing cell mass or volume.<sup>25</sup> Oral agents commonly prescribed for patients with type 2 diabetes do not prevent the progressive loss of  $\beta$ -cell function that is a feature of this disease.<sup>26</sup> The loss of  $\beta$ -cell function is correlated with increasing A1C levels and disease progression, which was demonstrated in the United Kingdom Prospective Diabetes Study (UKPDS).<sup>27</sup> The progressive nature of type 2 diabetes mandates a corresponding evolution of treatment. Most patients will ultimately require insulin therapy to maintain glycemic control.<sup>28</sup>

### Current diabetes management: Achievement and maintenance of glycemic control

There has been a gradual improvement in the achievement of glycemic control by patients with diabetes. However, results from the National Health and Nutrition Surveys (NHANES) indicate that current treatment still does not achieve glycemic control in a large percentage of patients. The rate of glycemic control, as defined by an A1C level <7%, increased from 35.8% in 1999 to only 57.1% in 2004.<sup>29</sup> Thus, despite a gradual improvement, antidiabetic therapy still fails to achieve the ADA/EASD target in more than 40% of patients.

### When do patients with type 2 diabetes become candidates for insulin therapy?

The most recent guidelines from the American Diabetes Association and the European Association for the Study of Diabetes recognize that insulin is the most effective diabetes medication for lowering hyperglycemia.<sup>24</sup> As noted above, the ADA/EASD treatment al-

gorithm now suggests that basal insulin can be added to the treatment regimen when a patient's A1C level remains  $\geq 7\%$  with lifestyle interventions and treatment with metformin.<sup>24</sup> Insulin may also be added when a combination of oral agents (eg, metformin and a sulfonylurea) does not maintain the A1C level at <7%. The ADA/EASD guidelines also recommend that insulin therapy be initiated immediately in patients with (1) severely uncontrolled diabetes with catabolism, defined as FPG >250 mg/dL, random glucose levels consistently >300 mg/dL, A1C >10%, or the presence of ketonuria; or (2) symptomatic diabetes with polyuria, polydipsia, and weight loss.<sup>24</sup>

Studies have shown that taking appropriate steps to achieve and maintain glycemic control can reduce the risk for long-term disease complications<sup>9-12</sup>; therefore, failure to take these steps, including failure to initiate insulin when necessary, and the resulting hyperglycemia likely increase the risk for long-term disease complications.

### Insulin preparations

The evolution of insulin preparations has greatly enhanced both the efficacy and safety of antihyperglycemic therapy.

#### Human insulins

Regular human insulin has been used to control prandial glucose (PG) excursions for many years, but because of its slow absorption and delayed onset of action,<sup>30</sup> it must be administered  $\geq 30$  minutes before meals.<sup>31</sup> Regular human insulin is also limited by the fact that absorption is variable and, therefore, it has variable efficacy in controlling PPG. The essential limitation of human insulin is that its pharmacokinetic/pharmacodynamic profile does not match that of physiologic insulin secretion in response to a meal.<sup>32</sup>

NPH, an intermediate-acting insulin, is generally used to provide a basal insulin level over the course of the day. However, the pharmacodynamic profile for this preparation poorly approximates physiologic insulin secretion.<sup>33</sup>

The onset of action of NPH begins approximately 2 to 4 hours after subcutaneous injection. There is a peak between 4 and 10 hours after injection that is followed by a slow decline. The total duration of action

for NPH insulin is 12 to 18 hours. Absorption of NPH insulin is also variable, both within and across patients.

Human insulins are also available in premixes designed to decrease the total number of daily injections required to control PG. These preparations may be useful in some patients because of their simplified dosing regimens. However, the pharmacokinetics for these preparations do not closely mimic patterns of physiologic insulin release, and they increase the risks of postprandial hyperglycemia and hypoglycemia.<sup>34</sup> Some of the limitations of premixed insulins have been addressed by using newer insulin analogs in these preparations (see below).

### Insulin analogs

Structural modifications made to the human insulin molecule have led to the development of insulin analogs. These structural modifications have resulted in improved pharmacokinetic/pharmacodynamic profiles that more closely mimic physiological insulin secretion, as well as improvements in efficacy and safety.<sup>35</sup> Currently available insulin analogs and premixes of these agents are listed in the **TABLE**.<sup>36</sup>

#### Rapid-acting insulin analogs

Rapid-acting insulin analogs more closely mimic physiologic insulin secretion compared with regular human insulin with respect to pharmacokinetic/pharmacodynamic profile, more rapid onset and shorter duration of action, greater peak effect, and better control over PPG.<sup>35-37</sup> When given at mealtimes, insulin lispro has consistently proven to be more effective than regular human insulin in lowering PPG. In addition, mealtime administration of insulin lispro improves glycemic control and reduces the risk for hypoglycemia compared with regular human insulin.<sup>38-41</sup> Insulin aspart has also been shown to provide improved control of PPG and reduced risk for hypoglycemia when compared with regular human insulin.<sup>42,43</sup> The third rapid-acting insulin analog currently available, insulin glulisine, has demonstrated improved or equivalent effects on 2-hour PPG excursions and overall glycemic control compared with regular human insulin.<sup>44</sup>

#### Long-acting insulin analogs

The 2 long-acting insulin analogs currently available are insulin glargine and insulin detemir. These agents have improved pharmacokinetic and pharmacody-

**TABLE**

**Insulin analogs and premixes currently available**

Analog	Trade name/ manufacturer
<b>Rapid-acting analogs</b>	
Lispro	Humalog/Eli Lilly
Aspart	Novolog/Novo Nordisk
Glulisine	Apidra/sanofi-aventis
<b>Long-acting analogs</b>	
Glargine	Lantus/sanofi-aventis
Detemir	Levemir/Novo Nordisk
<b>Premixed analogs</b>	
75% neutral protamine lispro, 25% lispro	75/25 Humalog/Eli Lilly
50% neutral protamine lispro, 50% lispro	50/50 Humalog/Eli Lilly
70% protamine aspart, 30% aspart	70/30 Novolog/Novo Nordisk

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namic characteristics, longer durations of action (up to 24 hours, allowing for once-daily dosing), less risk of hypoglycemia, and more predictable action than NPH insulin.<sup>45,46</sup> Insulin detemir is also associated with less weight gain than NPH insulin.<sup>45</sup> Insulin glargine has been shown to be as effective as bedtime NPH insulin in improving glycemic control, with less nocturnal hypoglycemia.<sup>47-49</sup> Insulin detemir has also been shown to be effective as basal insulin therapy in patients with type 2 diabetes and to have lower risk for hypoglycemia than NPH insulin.<sup>50-52</sup>

#### Premixes of insulin analogs

The limitations of human premixed insulins have been addressed by using newer insulin analog premix preparations. Analogues more closely approximate physiologic insulin secretion compared with human premix formulations, which reduces the risk for hypoglycemic episodes and provides more flexibility in dosing.<sup>34</sup> These newer biphasic insulin preparations have been shown to be effective for achieving glycemic control,<sup>53,54</sup> and they may also decrease the risk for hypoglycemia.<sup>55</sup> Specific subgroups of patients may be particularly suited

for treatment with premixes of insulin analogs. These include individuals with consistent mealtimes and lifestyles<sup>31</sup> and those whose adherence to treatment may be enhanced by a simple treatment regimen.<sup>34</sup>

### Benefits and risks/limitations of insulin therapy in patients with type 2 diabetes

Insulin, when properly dosed, is the most potent drug available to achieve tight glycemic control and avoid long-term disease complications.<sup>28</sup> The newer long- and rapid-acting insulin analogs and premixed insulin analogs have time-action profiles that more closely mimic physiologic insulin secretion than do human insulin formulations. These preparations provide

superior flexibility and convenience and thus may improve quality of life for patients.<sup>28</sup> Nevertheless, there are limitations associated with the use of insulin in general. Concern about hypoglycemia is an important barrier to insulin therapy, and weight gain is common among patients receiving insulin;<sup>56</sup> however, weight gain may also occur with some oral antidiabetic agents.<sup>57</sup> Insulin therapy also requires regular and frequent glucose monitoring<sup>58</sup> as well as increased patient involvement in the treatment regimen. Nevertheless, modern insulin treatment regimens are effective and well tolerated,<sup>59</sup> and because of the progressive nature of type 2 diabetes and the inevitable decline in  $\beta$ -cell function, such treatment is needed by most patients to maintain glycemic control.<sup>59</sup> ■

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**STUDY KEY**

**Abbreviations of studies mentioned in this article**

<b>ACCORD</b>	Action to Control Cardiovascular Risk in Diabetes study
<b>ADVANCE</b>	Action in Diabetes and Vascular Disease study
<b>DIGAMI 2</b>	Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction study
<b>HEART2D</b>	Hyperglycemia and Its Effect After Acute Myocardial Infarction on Cardiovascular Outcomes in Patients With Type 2 Diabetes study
<b>NHANES</b>	National Health and Nutrition Examination Surveys
<b>ORIGIN</b>	Outcome Reduction With Initial Glargine Intervention trial
<b>STOP-NIDDM</b>	Study to Prevent Non-Insulin-Dependent Diabetes Mellitus trial
<b>VADT</b>	Veterans Affairs Diabetes Trial
<b>UKPDS</b>	United Kingdom Prospective Diabetes Study

# Importance of daily plasma glucose control in type 2 diabetes

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## Normal physiologic pattern of insulin secretion

There are two characteristic features of the normal pattern of insulin secretion in healthy individuals<sup>1,2</sup>: a low-level basal insulin secretion that occurs continuously to maintain glycemic control between meals and an insulin spike that occurs rapidly in response to a caloric stimulus. After the prandial insulin surge, there is a prolonged insulin secretion that returns to basal levels after 2 to 3 hours (**FIGURE 1**).<sup>2</sup> Together, basal and prandial insulin secretions maintain control of glucose levels.

## Abnormalities in type 2 diabetes

Both insulin resistance and altered insulin secretion contribute to type 2 diabetes. Type 2 diabetes often occurs with obesity and an associated dysregulation of appetite. In the setting of genetic susceptibility, obesity can result in impaired insulin signalling, more commonly known as insulin resistance.<sup>3</sup> Patients with insulin resistance often progress to type 2 diabetes. The trigger for this progression is  $\beta$ -cell failure, involving partial loss of  $\beta$ -cell mass and deterioration of  $\beta$ -cell function.<sup>3</sup> Abnormalities in insulin secretion resulting from  $\beta$ -cell dysfunction in patients with type 2 diabetes include absence of pulsatility, loss of early-phase insulin secretion after meals, reduced basal and stimulated plasma insulin concentrations, and a progressive reduction in insulin secretory capacity with time and disease progression.<sup>4</sup> The decline in  $\beta$ -cell function and insulin secretion lead to a progressive loss of control over fasting plasma glucose (FPG) and postprandial glucose (PPG) and eventually to type 2 diabetes.<sup>4</sup>

The abnormalities characteristic of type 2 diabetes, most notably the decline in pancreatic  $\beta$ -cell function, are progressive.<sup>5</sup> In patients with this disease, along with accelerated  $\beta$ -cell apoptosis, there is a progressive decline in  $\beta$ -cell mass, replication, and regeneration. The loss of  $\beta$ -cell mass and function leads to the increase in glucose that is ultimately expressed as diabetes.<sup>5</sup> It is important to note that some aspects of  $\beta$ -cell dysfunction (eg, desensitization to stimulation by glucose) are reversible, while others (changes in gene expression with chronic exposure to high glucose concentrations) are not.<sup>6</sup> Autopsy studies report deficits in  $\beta$ -cell mass ranging from 0 to 65% in patients with type 2 diabetes.<sup>7</sup> Reduced  $\beta$ -cell function is also characteristic of individuals with prediabetes.<sup>8</sup>

## Postprandial glucose: A key determinant of outcomes in patients with type 2 diabetes

Both FPG and PPG are strongly correlated with glycosylated hemoglobin (A1C) levels,<sup>9,10</sup> and it has been shown that PPG is a stronger determinant of A1C levels than is FPG in patients with relatively well-controlled diabetes (A1C <7.3%).<sup>11</sup> In contrast, FPG increasingly contributes to increasing A1C levels in patients whose diabetes is poorly controlled.<sup>11</sup> As stated, A1C is strongly linked to risk for long-term microvascular and macrovascular complications of type 1 and type 2 diabetes, and there is cogent evidence to support the effectiveness of antihyperglycemic therapy in avoiding these adverse outcomes.<sup>12,13</sup>

### Contributions of FPG and PPG to long-term diabetes complications

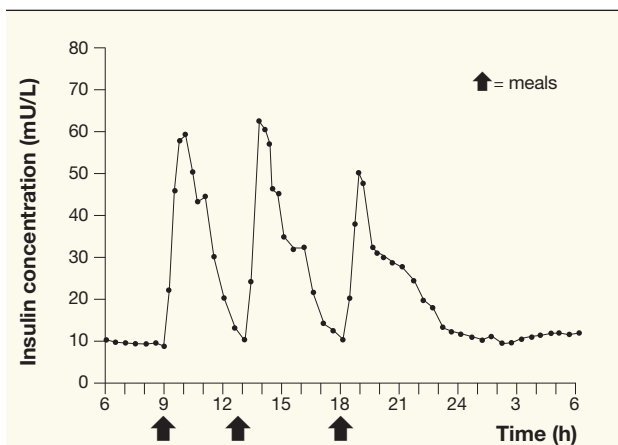
Both FPG and PPG have been demonstrated to be significant independent predictors of long-term complications in patients with type 2 diabetes. Results from multiple large-scale studies have demonstrated significant relationships between FPG and cerebrovascular events, cardiovascular events, heart failure, overt nephropathy, proliferative retinopathy, end-stage renal disease, and death.<sup>14-18</sup>

Postprandial hyperglycemia may play a particularly important role in diabetes-related cardiovascular risk. It has been shown to be a predictor of macrovascular complications (eg, myocardial infarction) and mortality in patients with type 2 diabetes.<sup>19-21</sup> In both the Honolulu Heart Study,<sup>20</sup> and the Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) study,<sup>19</sup> elevated PPG levels were associated with increased risk for fatal and total cardiovascular mortality.

Results from DECODE showed that elevated 2-hour postload glucose concentrations were correlated with an increased mortality risk that was independent of FPG.<sup>19</sup> Results from the Diabetes Intervention Study<sup>21</sup> showed that PPG was an independent risk factor for myocardial infarction and cardiovascular disease mortality in patients with type 2 diabetes. Results from the San Luigi Gonzaga study<sup>22</sup> demonstrated that PPG, but not FPG, was an independent risk factor for cardiovascular events in patients with type 2 diabetes, with a stronger predictive power in women than in men.

FIGURE 1

### Normal 24-hour physiologic insulin secretion



Phillips P. Insulins in 2002. *Australian Prescriber*. 2002;25:29-31. Reprinted with permission from Australian Prescriber. Copyright © 2002. National Prescribing Service.

### Plasma glucose variability

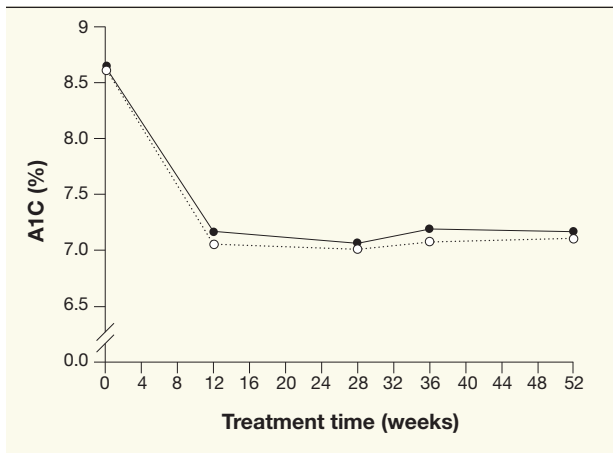
Recent analysis of glucose variability has determined that marked glycemic fluctuations are associated with an increased cardiovascular risk.<sup>23</sup> This may be associated with an increase in oxidative stress.<sup>24</sup> An increase in glucose variability is also correlated with higher central blood pressure.<sup>25</sup> All of these results underscore the importance of controlling FPG as well as the excessive PPG excursion so commonly seen in patients with diabetes.

### Mimicking physiologic insulin secretion for achievement of glycemic control

The American Diabetes Association treatment goal for patients with diabetes is A1C <7%.<sup>26</sup> Although this result may be achieved initially with dietary and lifestyle changes and oral antihyperglycemic medications, most patients will ultimately require insulin.<sup>27</sup> As discussed above, effective use of insulin must control both FPG and PPG to provide optimal risk reduction for long-term diabetes complications. Patient characteristics and habits, as well as the degree of disease progression, should guide the transition to insulin therapy in type 2 diabetes.<sup>27</sup>

### Making the transition

Several approaches can be used in making the transition from oral agents to insulin therapy in patients

**FIGURE 2****Change in A1C with addition of insulin detemir or insulin glargine to oral drug treatment**

A1C, glycosylated hemoglobin.

Black circles, insulin detemir; white circles, insulin glargine.

Reprinted with permission from Rosenstock J, et al. A randomised, 52-week, treat-to-target trial comparing insulin detemir with insulin glargine when administered as add-on to glucose-lowering drugs in insulin-naïve people with type 2 diabetes. *Diabetologia*. 2008;51:408-416. Copyright © 2008 Springer Berlin/Heidelberg.

with type 2 diabetes. Two commonly used approaches are the addition of basal insulin to ongoing oral therapy and the initiation of treatment with a pre-mixed insulin.

### Oral therapy plus basal insulin

The effectiveness of adding a long-acting insulin analog to oral therapy has been demonstrated in a 9-month, open-label, multicenter, observational study<sup>28</sup> in which add-on insulin glargine (dosed according to the judgment of the treating physician) was initiated in 12,216 patients with type 2 diabetes inadequately controlled with oral drugs. Study results showed that the addition of insulin glargine reduced A1C levels by 1.5% and fasting blood glucose (FBG) levels by 69 mg/dL without an increase in body mass index. A recent comparison<sup>29</sup> of glargine and detemir as add-on therapy to oral drug treatment in 582 patients with type 2 diabetes indicated that both agents were effective in lowering A1C and self-monitored FPG (FIGURE 2), with no difference in the relative risk for overall or nocturnal hypoglycemia. Among patients who completed the study, weight gain was slightly less with insulin detemir than with insulin glargine

(3.0 vs 3.9 kg, respectively).

For patients with type 2 diabetes who do not respond adequately to oral agents and lifestyle modification, insulin therapy may begin with the addition of a single evening dose of approximately 10 U of a long-acting insulin preparation, with weekly upward titration based on an FPG target of <100 mg/dL. In patients who experience hypoglycemia (FPG <72 mg/dL), titration should be discontinued for 1 week or the insulin dose reduced before being resumed. Once the target FPG level is obtained, titration can be maintained.<sup>30</sup> A simple insulin adjustment scale is vitally important for helping patients reach their target glucose levels once started on an insulin regimen. The algorithm will define both pre- and postmeal glucose targets and the method for achieving target control.

### Premixed insulins

Switching patients to a premixed insulin is also effective when glycemic control can no longer be maintained with oral therapy. Premixed analogs are available as 75% neutral protamine lispro suspension/25% insulin lispro mix (75/25), 50% neutral protamine lispro suspension/50% insulin lispro mix (50/50), and 70% insulin protamine aspart suspension/30% insulin aspart mix (70/30). Results from a study<sup>31</sup> in which a mixture of 75% neutral protamine lispro and 25% insulin lispro was substituted for glyburide showed that twice-daily administration of this preparation (morning and evening) for 4 months reduced A1C levels by 1.4% vs 0.7% in the glyburide group ( $P = .004$ ), FPG by 2.8 mmol/L (50.4 mg/dL) vs 1.1 mmol/L (19.8 mg/dL) ( $P < .01$ ), and evening 2-hour PPG by 4.4 mmol/L (79.2 mg/dL) vs 1.5 mmol/L (27.0 mg/dL) ( $P < .001$ ). Similar benefits have been demonstrated for insulin biphasic insulin aspart in a trial in which it was added to optimized treatment with metformin in a 34-week study that enrolled 191 patients with type 2 diabetes.<sup>32</sup>

### Next steps

#### Continued treatment with premixed insulin

Mixed formulations are a good choice for patients who eat meals on a regular schedule and whose lifestyles are more consistent day to day. These patients are not your “diet du jour” individuals, and they have little interest

in or aptitude for carbohydrate counting. Premixed insulins can be administered up to 3 times daily. A dose of premixed insulin may also be used at noon for those patients not achieving their A1C goal on a twice-daily regimen. With the appropriate guidance and education, patients will adjust their mealtime doses to fit the amount of calories consumed at the meal in question. Premixes containing regular human insulin should be administered 30 to 60 minutes prior to meals. This is a recommendation that is rarely followed for a variety of reasons. Analog mixtures can be taken within 15 minutes of a meal due to their rapid onset of action.<sup>1</sup>

A recent comparison<sup>33-35</sup> of premixed insulin analogs vs premixed human insulin formulations suggests similar effectiveness in lowering A1C and FPG levels, but superior effectiveness for premixed analogs in lowering PPG levels (**TABLE 1**).

Garber and colleagues have provided a simple and easy-to-follow approach for dosing premixed insulin analogs (**FIGURE 3**).<sup>36</sup> With this regimen, a biphasic preparation of insulin aspart (BIAsp30) is dosed initially once daily before dinner (12 U) along with oral therapy. If A1C remains >6.5%, oral secretagogues are discontinued and a second insulin dose is added at breakfast (3 U, if FBG is ≤110 mg/dL; 6 U, if FBG is >110 mg/dL). If A1C still remains >6.5%, a third insulin dose (3 U) is added at lunch. Clinical study results showed that 70% of patients using this premix twice daily achieved A1C ≤7.0 and 52% achieved A1C ≤6.5%. In addition, 77% of those taking this premix 3 times per day achieved A1C ≤7% and 60% achieved A1C ≤6.5%.

### Advancing basal insulin treatment

A summary of the approach for advancing a patient to basal-bolus insulin treatment is provided in the tear-off sheet at the end of the article. Several approaches can be taken to advance insulin therapy in a patient who has had basal insulin added to oral drugs. These include discontinuation of oral agents and initiation of treatment with a premixed insulin formulation or the addition of prandial insulin to basal insulin therapy. When basal insulin plus oral antihyperglycemic diabetic drugs are ineffective, a single dose of prandial insulin (ie, a rapidly acting analog) may be added before the largest meal of the day.

Additional prandial doses may be used to control postprandial hyperglycemia until the patient is

**TABLE 1**

### Comparison of premixed human insulins and premixed insulin analogs

Outcome	Comparative efficacy	Strength of evidence
FPG	Similar	Moderate
PPG	Favors insulin analogs	High
A1C	Similar	High
Hypoglycemia	Similar	High
Weight	Similar	Moderate

A1C, glycosylated hemoglobin; FPG, fasting plasma glucose; PPG, postprandial glucose.

Qayyum R, et al. *Ann Intern Med.* 2008;149:549-559. © 2008 Adapted with permission from *Annals of Internal Medicine*. The American College of Physicians is not responsible for the accuracy of the translation.

on 2 to 3 mealtime doses per day. These additions are made to keep postmeal glucose <180 mg/dL at midmorning or <140 mg/dL 2 hours after lunch or dinner.<sup>37</sup> Recommended starting doses of pre-meal rapid-acting insulins generally range from 5 to 10 U, or about 0.15 U/kg.

Several factors should be considered in subsequent dose titrations. For example, exercise improves insulin sensitivity; therefore, patients who engage in vigorous exercise within 3 hours of taking a dose of rapid-acting insulin may need to reduce that dose.<sup>38,39</sup> Because this effect is highly variable, titration must be carefully tailored to reflect the needs of the individual patient.

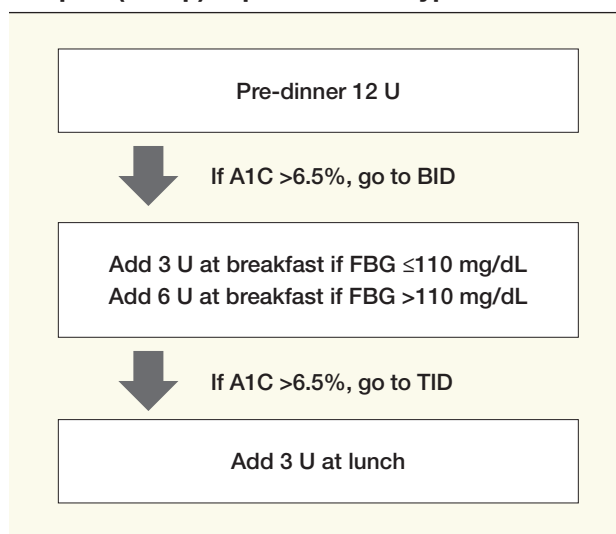
### Basal-bolus therapy

Basal-bolus therapy combines long- and rapid-acting insulin analogs; the long-acting agent is typically administered once daily and the rapid-acting agent is delivered at each meal.<sup>37</sup> The aim of this approach to treatment is to mimic normal physiologic insulin secretion and thus achieve near-normal glycemia.<sup>27,40</sup>

Basal-bolus therapy may provide the best approach to treatment for patients who vary their meal-times and/or the contents of those meals, or for those who eat only twice daily. A basal-bolus regimen may be particularly suitable for individuals whose jobs mandate variable meal patterns (eg, individuals who

**FIGURE 3**

**The 1-2-3 approach to dosing biphasic insulin aspart (BIAsp) in patients with type 2 diabetes**



FBG, fasting blood glucose (all doses should be taken pre-meal).  
 Garber AJ, et al. Attainment of glycaemic goals in type 2 diabetes with once-, twice-, or thrice-daily dosing with biphasic insulin aspart 70/30 (The 1-2-3 study). *Diabetes Obesity and Metabolism*. 2006;8:38-66.  
 Reproduced with permission from Blackwell Publishing Ltd.

must travel for work or have variable hours, shift workers). Many patients will prefer basal-bolus therapy because it provides increased flexibility with respect to the timing and content of their meals.<sup>27</sup>

One aspect of basal-bolus therapy that may be difficult for some patients is determining the carbohydrate content for a given meal and adjusting their prandial insulin dose accordingly. It has been suggested that barriers to basal-bolus therapy related to carbohydrate counting include difficulties patients may have calculating mealtime carbohydrates and the education/resources needed to set the stage for this form of intensive insulin treatment.<sup>41</sup> However, there are simple alternatives to carbohydrate counting for patients who have difficulty with this requirement. A recent study by Bergenstal et al<sup>42</sup> showed that adjusting bolus insulin according to a simple algorithm based on whether mealtime glucose levels were above or below target (TABLE 2) was as effective as carbohydrate counting for controlling A1C and FPG in patients with type 2 diabetes. Furthermore, there were no significant differences between treatments in PPG levels.<sup>42</sup> It is also worth noting that patients in this trial who counted carbohydrates were able to effectively adjust their

insulin doses and experienced less weight gain than the patients who used the simple algorithm.<sup>42</sup>

**Insulin pens and pumps**

Insulin pens may facilitate both compliance and effective insulin treatment of patients with type 2 diabetes. These devices are either reusable with replaceable insulin cartridges or disposable. They typically feature dose selectors and a discreet appearance, and are generally viewed as being easy for patients to use and preferred by them over syringes and vials.<sup>43</sup>

Insulin pumps provide another alternative for the delivery of intensive insulin therapy.<sup>44</sup> Insulin pumps have been used effectively in patients with type 2 diabetes and they may provide multiple benefits, including enhanced reproducibility of insulin delivery and attenuation of the “dawn” phenomenon (the increase in PG levels in the morning). In comparison to multiple daily injections, insulin pumps may provide greater flexibility with respect to the timing of meals and snacks, programmable basal rates to optimize overnight glycemic control, the ability to reduce the risk of exercise-induced hypoglycemia, and enhancement of the patient’s ability to control his or her own diabetes.<sup>45</sup> There is also evidence that pumps may permit achievement of lower A1C levels than do multiple daily insulin injections.<sup>46</sup> Furthermore, it appears that the benefits of continuous insulin delivery are enhanced with a rapid-acting insulin analog vs regular human insulin.<sup>47</sup> Results from one clinical trial that compared insulin pump treatment to multiple daily injections in patients with type 2 diabetes indicated that 93% of pump-treated patients preferred it to their previous injectable insulin regimen for reasons of convenience, flexibility, and ease of use.<sup>48</sup> There are potential disadvantages associated with insulin pumps. Patients may object to having an infusion device attached to their body. Successful insulin pump therapy requires appropriate patient selection, effective education, and patient commitment to intensive self-monitoring blood glucose (SMBG).<sup>49</sup>

There are currently 3 continuous glucose monitoring (CGM) devices available for use, along with the insulin pumps available on the market. These pumps, which are sensor augmented, receive glucose data from a subcutaneous sensor every 5 minutes. A recent comparison of an insulin pump with CGM vs an insulin

**TABLE 2**

**Simple approach to determining mealtime insulin dosing  
with a rapid-acting insulin analog in basal-bolus therapy**

<b>Mealtime dose</b>	<b>Pattern of mealtime blood glucose values below target<sup>a</sup></b>	<b>Pattern of mealtime blood glucose values above target<sup>b</sup></b>
≤10 units	Decrease by 1 unit	Increase by 1 unit
>11-19 units	Decrease by 2 units	Increase by 2 units
≥20 units	Decrease by 3 units	Increase by 3 units

<sup>a</sup> If more than one-half of the mealtime blood glucose values for the week were below target.

<sup>b</sup> If more than one-half of mealtime blood glucose values for the week were above target.

Bergenstal RM, et al. Copyright © 2008 American Diabetes Association. From *Diabetes Care*, Vol. 31; 2008, 1305-1310. Reprinted with permission from The American Diabetes Association.

pump with SMBG indicated no significant difference between treatments with respect to decline in A1C levels, but there was an increased risk for hypoglycemia in the pump with SMBG group.<sup>50</sup>

Other problems that have become less common with newer pumps and insulin preparations include catheter occlusions due to instability of insulin and formation of precipitates.<sup>51</sup> Rapid-acting insulin analogs have good temperature stability and low risk for catheter occlusion.<sup>51,52</sup> It has also been shown that overnight interruption of infusion with a rapid-acting insulin analog is not associated with a higher risk for metabolic decompensation vs regular human insulin.<sup>53</sup> Pump advocates contend that insulin pumps offer a more convenient way to deliver intensive insulin management than self-administration of multiple injections.

It should be noted that Medicare has relaxed the criteria for reimbursement for insulin pumps. A new pump patient must complete a diabetes education program, require ≥3 insulin injections per day, and make frequent self-adjustments of insulin for ≥6 months before initiating pump therapy. The patient must have documentation of need to self-monitor

BG ≥4 times a day for ≥2 months prior to pump treatment and meet at least one of the following criteria while on multiple daily injection treatment: A1C >7.0%, recurring hypoglycemic episodes, wide fluctuations of BG prior to meals, experience the “dawn” phenomenon (FBG >200 mg/dL, or a history of severe glycemic excursions). The C-peptide criterion for pump use is <110% of the laboratory’s lower limit of normal for patients with normal renal function.<sup>45</sup>

### Conclusions

Because of the progressive loss of β-cell function and the decline in the ability of the pancreas to produce insulin, most patients with type 2 diabetes eventually will require insulin therapy. There are several approaches for transitioning the patient from oral agents to insulin therapy, and the goal of insulin treatment for the patient who has made this switch is to provide exogenous insulin in a manner that mimics normal physiologic insulin secretion. Basal-bolus treatment with long- and rapid-acting insulin analogs is capable of achieving this goal. ■

TEAR-OFF SHEET

## Suggestions for progressive insulin treatment: Basal-bolus therapy

### Addition of basal insulin to oral therapy

A single dose of approximately 10 U of a long-acting insulin preparation may be added in the evening.

- Titrate upward weekly based on an FPG target of <100 mg/dL.
- In patients who experience hypoglycemia (FPG <72 mg/dL), titration should be discontinued for 1 week or the insulin dose reduced before being resumed.
- Once the target FPG level is obtained, titration can be maintained.

### Progressive treatment intensification to basal-bolus therapy when basal insulin and oral drugs no longer provide glycemic control

A single dose of prandial insulin (ie, a rapidly acting analog) may be added before the largest meal of the day.

- Additional prandial doses may be used to control postprandial hyperglycemia until the patient is on 2 to 3 mealtime doses per day.
- Recommended starting doses of premeal rapid-acting insulins generally range from 5 to 10 U, or about 0.15 U/kg.
- Keep postmeal glucose <180 mg/dL at midmorning or <140 mg/dL 2 hours after lunch or dinner.

FPG, fasting plasma glucose.

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# When and how to implement basal-bolus therapy: Treating to success

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## Most patients with diabetes will require insulin therapy

The majority of patients with longstanding diabetes are candidates for insulin therapy,<sup>1</sup> as a substantial proportion of pancreatic  $\beta$ -cell function has been lost by the time the disease is diagnosed. Results from one recent study indicated that, at the time of diagnosis, most patients with type 2 diabetes had already lost 80% of their  $\beta$ -cell function.<sup>2</sup> It has further been shown that  $\beta$ -cell function begins to decline in patients with insulin resistance prior to the emergence of impaired glucose tolerance.<sup>3</sup> During the early stages of type 2 diabetes, lifestyle interventions (including modifications to diet and exercise patterns) may be successful for improving glycemic control for some patients.<sup>4</sup> However, as  $\beta$ -cell function continues to decline, pharmacologic treatment, consisting of combination therapy with 2 or 3 oral antihyperglycemic agents, in addition to lifestyle modifications, is often required.<sup>5</sup> When oral agents are not effective in reaching A1C targets, addition of insulin therapy is required.<sup>6</sup> Indeed, by 6 years after initiation of treatment with oral agents, about one-half of patients will require insulin treatment.<sup>1</sup> With the recent information by DeFronzo suggesting that 80% of a patient's  $\beta$ -cell function has been lost by the time of diagnosis,<sup>2</sup> insulin therapy may be indicated even earlier in the management of type 2 diabetes.

Because  $\beta$ -cell failure is progressive and most patients with type 2 diabetes will ultimately require insulin therapy, there is an emerging awareness that using insulin earlier in the course of the disease is physiologically sound and should be an integral part of adequate diabetes management.<sup>7</sup> Therapy for patients with diabetes should be aimed at "treating to target," using information gained from careful patient monitoring.<sup>8</sup> With this approach, treatment should be directed at a specific A1C goal and promptly adjusted as needed to reach the target. This approach is in contrast to a slower stepwise approach, which is likely to result in repeated failure and loss of glycemic control. Treating to target is particularly important because of the progressive nature of diabetes, with increasing insulin resistance and decreasing insulin secretion over time. As the disease progresses, so should therapy.

## Treatment progression in patients with diabetes

The remainder of this article presents information about management of type 2 diabetes in the face of progressive loss of  $\beta$ -cell function and declining production of endogenous insulin.

## CASE STUDY

A 41-year-old African American woman presents to her primary care physician for her annual physical examination. Her medical history includes two normal pregnancies with delivery of healthy children and hypertension with blood pressure controlled by a combination of valsartan and hydrochlorothiazide. The patient smokes cigarettes (one-half pack per day) but does not consume alcohol. Physical examination reveals an overweight woman with no other abnormalities. The patient's vital signs and laboratory values are summarized in TABLE 1.

The patient's A1C and fasting plasma glucose (FPG) levels are consistent with a diagnosis of diabetes. A repeat evaluation of FPG carried out 3 days after the initial evaluation resulted in an FPG of 131 mg/dL, confirming a diagnosis of diabetes.<sup>9</sup> Initial treatment is consistent with the recommendations of the American Diabetes Association (ADA) and includes dietary and lifestyle changes and pharmacotherapy with metformin (1000 mg/day).<sup>6,9</sup> Atorvastatin is also initiated at a dose of 10 mg/day in accordance with ADA recommendations for treatment of dyslipidemia.<sup>9</sup> This regimen is continued for 2 years with titration of metformin to 2000 mg/day and continuation of atorvastatin at the initial dose. At the end of 1 year, A1C had declined to 7.1% and low-density lipoprotein cholesterol (LDL-C) was reduced to 97 mg/dL. The patient's body weight decreased to 157 lb. By 2 years, A1C had increased to 7.9%, LDL-C remained stable at 98 mg/dL, and body weight increased slightly to 161 lb. The increase in A1C prompted addition of glyburide (initial dose 5 mg/day, titrated to 20 mg/day) to the treatment regimen. Follow-up 6 months later demonstrated a decline in A1C to 7.3%, but further follow-up at 1 year showed that A1C had again increased to 8.0%. At this point, a decision is made to initiate insulin therapy. This change in treatment is consistent with ADA recommendations.<sup>6</sup>

### Initiation of insulin therapy

There are multiple approaches to the initiation of insulin therapy in a patient with type 2 diabetes who

TABLE 1

Case study: Baseline vital signs and clinical laboratory values

Vital signs		Laboratory values	
Height	5 ft, 7 in	A1C	8.4%
Weight	159 lb	FPG	129 mg/dL
Temperature	98.7°F	Lipid panel: Total cholesterol	178 mg/dL
		LDL-C	134 mg/dL
		HDL-C	54 mg/dL
		Triglycerides	141 mg/dL
Blood pressure	139/91 mm Hg	Hematology	Normal
Pulse rate	74 bpm	Blood chemistry	Normal
Respiratory rate	19 breaths/min	Urinalysis	Normal

A1C, glycosylated hemoglobin; FPG, fasting plasma glucose; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

can no longer maintain glycemic control on oral agents. In this case, the decision is made to add basal insulin and continue treatment with oral drugs. This approach is consistent with results from clinical trials that have shown that adding basal insulin to ongoing oral therapy can improve glycemic control.<sup>10</sup> The improvement in glycemic control achieved with the addition of basal insulin is believed to result from suppression of overnight hepatic glucose production, both through direct effects on the liver and indirect effects due to inhibition of free fatty acid release by adipose tissue.<sup>11</sup>

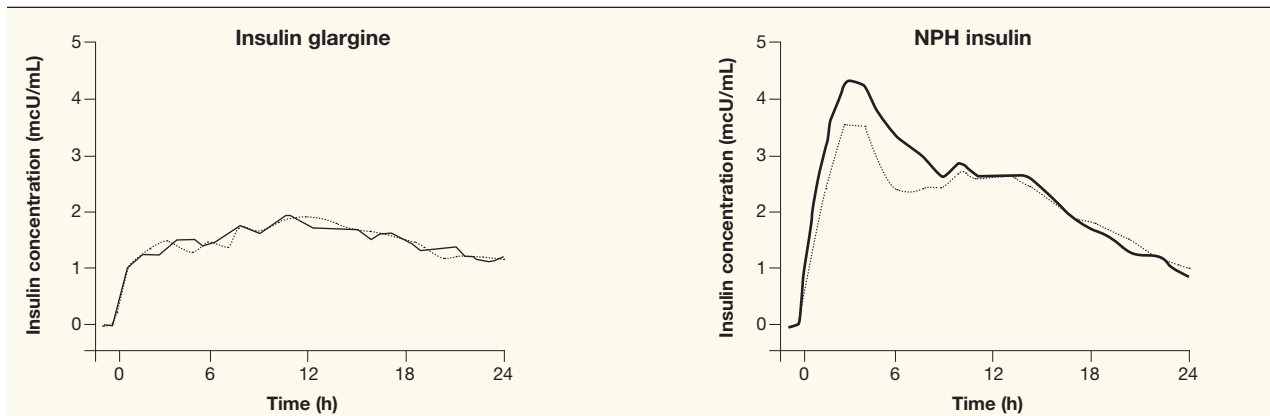
### Basal insulin properties

The two main options for basal insulin therapy are neutral protamine Hagedorn (NPH) insulin or a long-acting insulin analog (insulin glargine or insulin detemir). The pharmacokinetic/pharmacodynamic profiles for NPH insulin and long-acting insulin analogs are substantially different (FIGURE). Those for the long-acting insulin analogs are relatively flat, while those for NPH insulin have a distinct peak at about 4 hours.<sup>12</sup>

These differences in time-action profiles affect both dosing requirements and clinical efficacy. Insulin with an intermediate duration of action (13 to 16 hours), such as NPH insulin, must be given in the evening or at bedtime and often requires twice-daily administration, with a second dose in

## FIGURE

## Pharmacokinetic profiles for insulin glargine and NPH insulin



NPH, neutral protamine Hagedorn. The solid and dashed lines represent 2 different study days.

Scholtz HE, et al. *Diabetologia*. 2005;48:1988-1995. Reprinted with permission from *Diabetologia*. Copyright © 2005 Springer Verlag.

the morning. Long-acting insulin analogs can be administered at bedtime, before dinner, or in the morning, due to their longer durations of action and lower peak effects.<sup>11</sup>

The pharmacokinetic effects of NPH insulin are also more variable than those of insulin glargine or insulin detemir. This is the case within patients even when the insulin is injected at the same site from one day to the next. This variability is a result of the manner in which NPH insulin is structured.<sup>13</sup> Protamine is added to regular insulin to extend its duration of action. Protamine ionizes the insulin molecule, which forms a complex with itself to remain in a hexameric structure at the injection site, resulting in a longer duration of action and longer time to peak. However, the resulting poor solubility of this insulin preparation increases the variability in its pharmacokinetic profile. The requirement for resuspension of NPH insulin prior to injection may also contribute to inter- and inpatient variability in the action of this insulin because the actual amount of insulin administered may vary from one injection to the next.<sup>13</sup> This high variability is not observed with long-acting insulin analogs,<sup>13</sup> which may contribute to the lower risk for hypoglycemia with these agents versus NPH insulin.<sup>8</sup> Results from multiple clinical studies have demonstrated the effectiveness of adding a long-acting basal insulin analog to oral therapy in patients with type 2 diabetes.<sup>8,14-16</sup> Furthermore, a recent comparison of long-acting insulin analogs used in addition to oral agents indicated similar efficacy and safety; however,

insulin detemir was associated with less weight gain than insulin glargine.<sup>17,18</sup>

#### Basal insulin dosing regimens

Dosing regimens for long-acting insulin analogs are straightforward. The initial dose for insulin detemir is usually 10 U.<sup>19</sup> In the PREDICTIVE 303 study, patients self-adjusted their insulin detemir dose every 3 days based on the average of 3 self-monitored blood glucose (SMBG) values. Insulin detemir doses were adjusted as follows: if the mean FPG is <80 mg/dL, the dose is reduced by 3 U; if the mean FPG is 80 to 110 mg/dL, there is no change in dosing; and if the mean FPG is >110 mg/dL, the dose is increased by 3 U.<sup>20</sup> Another recent study demonstrated that patients can safely self-titrate insulin detemir to an FPG target of 70 to 90 mg/dL with low rates of hypoglycemia.<sup>21</sup>

The typical initial dose for insulin glargine is 10 U.<sup>22</sup> In one study, doses for insulin glargine were adjusted as follows: no change is required if FPG remains between 70 and 94 mg/dL; if FPG is <70 mg/dL for 3 days, the dose should be decreased by up to 10% of the total dose; and if FPG is 95 to 119, 120 to 139, 140 to 180, or >180 mg/dL for 3 days, the dose should be increased by 2, 4, 6, or 8 U, respectively.<sup>23</sup>

#### Intensifying treatment with basal-bolus administration of long- and rapid-acting insulin analogs

Although the addition of basal therapy is highly effective in many patients, the progressive nature of diabetes may require further intensification of treatment.

## CASE STUDY

The patient had insulin glargine (initial dose 10 U) added to ongoing oral therapy, and follow-up at 6 months indicated that her A1C level had declined to 7.1%. However, after an additional year of treatment, her A1C increased to 7.8%. This increase prompted consideration of intensification of the treatment regimen with the addition of bolus insulin.

Rapid-acting insulin analogs are a suitable first choice for intensification of therapy. Rapid-acting insulin analogs have lower variability in absorption and more consistent pharmacodynamic profiles than regular human insulin.<sup>24,25</sup> Rapid-acting insulin analogs provide higher 1- and 2-hour insulin values and reduced risk for late postprandial hypoglycemia due to a shorter duration of action, and may provide quality-of-life benefits due to greater flexibility in timing and dosing (eg, dosing with meals versus regular human insulin, which requires dosing 30 to 45 minutes prior to meals).<sup>26</sup> These insulin analogs provide a more physiologic action that coincides with meal patterns.

### Stepwise initiation of basal-bolus therapy

Adding prandial insulin to basal insulin may be considered the best way to restore postprandial and overall glycemic control when the combination of basal insulin and oral therapies is no longer sufficient. However, making an immediate transition from a basal (or premixed) insulin regimen to a more complex basal-bolus regimen is challenging. Stepwise addition of prandial insulin to basal insulin may be considered a more practical alternative than using multiple daily injections.<sup>11</sup> In many cases, a single mealtime prandial injection of a rapid-acting insulin analog that controls the highest postprandial glucose (PPG)—often associated with the largest meal—might be sufficient to restore glycemic control.<sup>27</sup> The prandial insulin dose can then be titrated in accordance with SMBG values measured 2 hours after the start of the meal, before the next meal, or at bedtime if the injection is administered before the evening meal. The prandial insulin dose can be adjusted independently to limit postprandial hyperglycemia without affecting basal insulin action.<sup>11,27</sup> A simple dose titration scheme for both basal

and prandial insulin analogs is provided in a tear-off sheet at the end of this article.

### Initiation of basal-bolus therapy

A logical treatment progression for a patient who has had prandial insulin added to the treatment regimen is transition to basal-bolus therapy. The initial total daily insulin dose is 0.5 U/kg.<sup>28</sup> In these regimens, basal and bolus insulin requirements are each approximately half of the total daily insulin needed. The total dose of rapid-acting insulin analog is divided, with 38% delivered at breakfast, 28% at lunch, and 33% at dinner (White RD, et al. Unpublished data). The reason that the highest prandial dose is delivered at breakfast is based not only on the carbohydrate content of the meal but also on the “dawn phenomenon,” a morning surge in plasma glucose that occurs secondary to a physiologic morning rise in cortisol and growth hormone levels. Carroll et al found that this phenomenon occurs in 55% of patients with type 2 diabetes.<sup>29</sup> Patients who do not experience this morning glucose surge may have one-third of their prandial insulin dose administered at each meal.

A patient can begin insulin therapy with one evening dose of a long-acting insulin (approximately 10 U) with the dose adjusted as described above.<sup>20,23</sup> Insulin levels should be titrated until the patient’s FPG is between 70 and 130 mg/dL. If a patient experiences hypoglycemia (FPG <70 mg/dL), bedtime insulin must be reduced by  $\geq 4$  U, or by 10% if the dose is >60 U, to minimize these events.<sup>30</sup>

Rapid-acting insulin analogs have accelerated pharmacokinetics compared with long-acting insulins, and they require adjustments that can be made at shorter intervals. Many factors should be considered when titrating an insulin dose. For example, exercise improves insulin sensitivity, and it is often necessary to reduce the insulin dose in patients who engage in moderate or strenuous exercise.<sup>31</sup>

Carbohydrate counting is an alternative to dosage algorithms for determining prandial insulin dose and it provides for more flexibility in meal planning,<sup>23</sup> but this is not absolutely necessary. An example of a carbohydrate-counting method that has been used in combination with prandial insulin glulisine is shown in **TABLE 2**.<sup>23</sup>

SMBG should be carried out 3 or more times daily for patients using multiple insulin injections.<sup>9</sup> To achieve

TABLE 2

Example of carbohydrate counting and insulin glulisine dose adjustment<sup>a</sup>

Mealtime dose	Pattern of mealtime glucose values below target <sup>b</sup>	Pattern of mealtime glucose values above target <sup>c</sup>
1 U/20 g CHO	Decrease to 1 U/25 g CHO	Increase to 1 U/15 g CHO
1 U/15 g	Decrease to 1 U/20 g	Increase to 1 U/10 g
1 U/10 g	Decrease to 1 U/15 g	Increase to 2 U/15 g
2 U/15 g	Decrease to 1 U/10 g	Increase to 3 U/15 g
3 U/15 g <sup>d</sup>	Decrease to 2 U/15 g	Increase to 4 U/15 g

CHO, carbohydrate.

<sup>a</sup> Each patient in the carb count group was also given a schedule for a mealtime insulin glulisine correction dose to add a few units if high or subtract a few units if low.

<sup>b</sup> If more than one-half of the mealtime blood glucose values for the week were below target.

<sup>c</sup> If more than one-half of the mealtime blood glucose values for the week were above target.

<sup>d</sup> Increase mealtime insulin as needed following this pattern.

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PPG targets, postprandial SMBG may be appropriate.<sup>9</sup> Concern about hypoglycemia is a significant psychological barrier to intensive insulin therapy,<sup>32</sup> but this risk is reduced by the use of modern long- and rapid-acting insulin analogs. For example, in one study, switching patients from the combination of regular human insulin and NPH insulin to insulin lispro and insulin glulisine resulted in a 44% reduction in the occurrence of hypoglycemia.<sup>33</sup> Results from a second comparison of these combinations for intensive insulin therapy indicated a 43% reduction in the occurrence of nighttime hypoglycemia with the insulin analogs.<sup>34</sup> The combination of insulin detemir and insulin aspart has also been associated with a 38% lower risk for nighttime hypoglycemia vs NPH insulin plus regular human insulin in patients receiving basal-bolus treatment.<sup>35</sup>

### Practical considerations for treating to target with basal-bolus therapy

A number of actions can increase the probability of reaching treatment targets in patients receiving basal-bolus therapy. Treatment regimens must be made as simple as possible to increase the possibility of adherence and therefore A1C goal attainment.<sup>27</sup> Advances in therapy may help in this process. Rapid-acting insulin analogs that can be administered shortly before or even after meals<sup>36</sup> have the potential to improve adherence.

Adherence to treatment in difficult-to-manage patients may also be improved with multisystemic therapy, an intensive home- and community-based psychological intervention originally used with youths presenting with serious mental health problems and their families. Multisystemic therapy has been shown to improve treatment adherence in patients with type 1 diabetes.<sup>37</sup>

Patient referral to specialists for intensive diabetes care may be necessary to reach treatment targets in some patients. A study by Graber et al,<sup>38</sup> suggests that referral of patients with unsatisfactory glycemic control, frequent hypoglycemia, or inadequate self-management to a diabetologist-directed team of nurse and dietitian educators for intensive diabetes care may significantly improve adherence and glycemic control.<sup>38</sup>

Additional practical steps that may increase the probability of reaching treatment goals include monitoring A1C levels every 3 months in addition to SMBG; aggressively managing hyperglycemia, dyslipidemia, and hypertension with the same intensity to obtain the best patient outcomes; addressing the underlying pathophysiology, including the treatment of insulin resistance; initiating combination therapy or insulin immediately for all patients with A1C  $\geq 9\%$  at diagnosis; and implementing a multidisciplinary and interdisciplinary team approach to diabetes management, both to encourage patient education and self-care and to share responsibility with patients in achieving their glucose goals.<sup>39</sup>

TEAR-OFF SHEET

## Dosing titration for insulin analogs

BG levels for 3 consecutive days (fasting, prandial, or bedtime)	Adjust basal insulin dose (U)	Adjust rapidly acting insulin dose (U/injection)
≥180 mg/dL	+8	+3
160-180 mg/dL	+6	+2
140-160 mg/dL	+4	+2
120-140 mg/dL	+2	+1
100-120 mg/dL	+1	Maintain dose
80-100 mg/dL	Maintain dose	-1
60-80 mg/dL <sup>a</sup>	-2	-2
<60 mg/dL <sup>a</sup>	-4	-4

BG, blood glucose; FBG, fasting blood glucose.

<sup>a</sup>If any single blood glucose measurement is in this range, make the appropriate reduction in insulin dose.

For elevated FBG levels, adjust only the basal insulin dose.

For elevated preprandial BG at lunchtime, adjust breakfast rapid-acting insulin dose.

For elevated preprandial BG at dinnertime, adjust lunchtime rapid-acting insulin dose.

For elevated bedtime BG, adjust dinnertime rapid-acting insulin dose.

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# Overcoming barriers to insulin replacement

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## The typical approach to treatment for the patient with type 2 diabetes

The currently recommended approach to treatment for the typical patient who is newly diagnosed with type 2 diabetes follows specific steps.<sup>1</sup> Oral metformin therapy and lifestyle modifications comprise the first step. These interventions should be initiated at diagnosis, with metformin titrated aggressively to achieve glycemic control.<sup>1</sup> Because of disease progression and the loss of  $\beta$ -cell function over time, further treatment is usually needed to achieve glycemic goals, and most patients will ultimately require insulin therapy.<sup>2,3</sup> Making the transition to insulin therapy is a critical step in the management of patients with type 2 diabetes; however, both primary care clinicians (PCCs) and patients are often reluctant to make this switch in treatment.<sup>3</sup> In fact, treatment trends indicate that insulin use is declining in patients with type 2 diabetes.<sup>4</sup> This article reviews barriers to effective insulin therapy and achievement of glycemic control in patients with type 2 diabetes, including barriers related to clinicians, health care systems, patients, and medications, as well as approaches to overcoming them.

## Barriers to effective insulin therapy

### Clinician-related barriers

There are several important clinician-related barriers to effective insulin therapy. Because PCCs manage most patients with type 2 diabetes, therapeutic success must not be obstructed by an unnecessarily pessimistic attitude: that the disease inherently carries very high and “unavoidable” risks, or that achieving treatment goals does not meaningfully reduce these risks. Due at least in part to these beliefs, PCCs may treat patients with diabetes less aggressively than do specialists. They are less likely to use insulin therapy and, in contrast to diabetes specialists, they tend to intensify treatment more slowly.<sup>5-7</sup> Clinical inertia also contributes significantly to clinicians’ reluctance to initiate insulin therapy in patients whose diabetes is not controlled with oral agents.<sup>6</sup> A prospective observational study<sup>8</sup> compared treatment intensification and glycemic control in a general medical clinic supervised by internal medicine faculty with a diabetes clinic supervised by endocrinologists. Both clinics served similar populations. Patient demographics were similar

for the 2 treatment settings, but glycosylated hemoglobin (A1C) levels averaged 8.6% in the general medical clinic vs 7.7% in the diabetes clinic. Intensification of therapy for patients with elevated glucose levels was about 50% less likely in the general medical clinic than in the diabetes clinic, yet intensification of therapy was independently associated with improvement in A1C levels.

Another barrier to insulin therapy that might be considered clinician related is the historic lack of guidelines encouraging the early use of insulin therapy in patients with type 2 diabetes. This problem has been overcome with the most recent ADA/EASD guidelines, which recommend insulin as a preferred second step for patients who are not controlled by the combination of dietary and lifestyle changes and pharmacotherapy with metformin.<sup>1</sup>

### Health system-related barriers

The health care system creates significant barriers to effective insulin therapy in patients with type 2 diabetes, of which the most important may be the cost of care and the need for insurance coverage.<sup>9</sup> Although certified diabetes educators (CDEs) provide a wealth of information for diabetes patients, failure to refer to CDEs, unavailability in some areas, failure of some organizations to provide reimbursement for the education they give to patients, and overreliance on a single educational experience rather than periodic educational updates may leave the patient who has diabetes inadequately prepared to meet the progressive demands of the disease. In a survey study by Oliveria et al,<sup>10</sup> 47.1% of patients (discontinuers) indicated that their doctor advised against using insulin, while 86.1% of non-initiators were never advised by a health care provider to take insulin. State laws prohibiting patients who are taking insulin from engaging in certain occupations (eg, driving commercial vehicles) are an obstacle to some.

### Patient-related barriers

Patient-related barriers are also a significant cause for failure to achieve glycemic control with either oral or insulin therapy. Failure to achieve glycemic control is often due to poor treatment adherence. A recent review of the literature (1993 to 2003) by Cramer et al<sup>11</sup> indicated that adherence to insulin treatment among patients with type 2 diabetes was 62% to 64%, while

adherence to oral therapy ranged from 36% to 93%. Specific patient-related barriers to initiation and achievement of glycemic control with insulin therapy include complex and inconvenient treatment regimens, lack of knowledge of underlying pathophysiology of their disease and the need for insulin, a desire to avoid needles, concerns about insulin-associated hypoglycemia and weight gain, and fear of complications erroneously believed to be associated with insulin treatment.<sup>3,5,12</sup>

Fear of hypoglycemia is a particularly important patient-related barrier, and it is the most recognized adverse effect associated with intensive insulin therapy.<sup>3</sup> Reducing risk for hypoglycemia was considered to be an important determinant of treatment success with basal insulin therapy in the Treat-to-Target study.<sup>2</sup> Specific patient characteristics may raise barriers to effective antidiabetic therapy. Any time there is a language barrier, it is more difficult for PCCs to address potential negative perceptions; for instance, one report on insulin therapy in Latino patients identified poor communication as a culprit in creating misperceptions.<sup>13</sup> Comorbid depression may also interfere with adherence to therapy. Results from a study of 4463 patients with diabetes indicated that major depression was associated with poorer performance of patient-initiated behaviors that included exercise, diet, and medication adherence.<sup>14</sup>

### Medication-related barriers

Both clinicians and patients often believe that starting insulin may be too complicated.<sup>3</sup> PCCs may also be uncertain as to the best way to initiate insulin treatment.<sup>3</sup> Patients may also have concerns about the need to self-inject using a vial and syringe in public places.<sup>3</sup>

The properties of specific insulins and the resulting requirements for administration, as well as the risk for adverse events, are also potential barriers to the achievement and maintenance of glycemic control.<sup>15,16</sup> The properties of different insulins are described in detail in the preceding articles in this supplement, and they are considered only briefly here.

### Concerns about hypoglycemia

Hypoglycemia is traditionally defined by the development of autonomic symptoms (eg, hemodynamic changes, cardiac dysrhythmias) as well as neuroglycopenic symptoms (eg, cognitive impairment, mood

swings), a low plasma glucose level, and reversal of symptoms as blood glucose levels return to normal.<sup>17,18</sup> The ADA provides guidance on the classification of hypoglycemia.<sup>19</sup> Severe hypoglycemia is an event requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions; glucose levels are usually <56 mg/dL. Severe hypoglycemic episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. Documented symptomatic hypoglycemia is an event with typical symptoms and a measured plasma glucose concentration  $\leq 70$  mg/dL. Probable symptomatic hypoglycemia is an event during which symptoms of hypoglycemia are not accompanied by a plasma glucose determination but one that was presumed to be caused by a glucose concentration  $\leq 70$  mg/dL. Asymptomatic hypoglycemia is a plasma glucose concentration  $\leq 70$  mg/dL without symptoms. Relative hypoglycemia is the occurrence of the typical symptoms of hypoglycemia but with a measured plasma glucose level >70 mg/dL (eg, symptoms associated with a rapid decline in glucose, such as a reduction in glucose from 200 mg/dL to 100 mg/dL over a very brief time period).

Both regular human and NPH insulins are associated with a relatively higher risk for hypoglycemia compared with insulin analogs.<sup>20</sup> Patients' reasonable concerns about these events, perhaps based on stories of friends or family using the older insulin formulations, may result in reluctance to initiate insulin therapy.<sup>3</sup> Education about best management of hypoglycemia, as well as assiduous attention to pharmacotherapy that avoids hypoglycemia, are the best preventive steps.<sup>21</sup>

### **Weight gain**

Insulin therapy commonly results in weight gain in patients with diabetes. Concern about weight gain and its potential health consequences can be a barrier to initiation or intensification of insulin therapy. It can also negatively affect adherence to prescribed treatment.<sup>22</sup>

## **Overcoming barriers**

### **Clinician-related barriers**

More effective education for PCCs can help lower barriers to effective insulin therapy and improve glycemic control in their patients.<sup>23</sup> With more knowledge, PCCs can also more effectively educate their patients with

diabetes about the disease. Furthermore, a study by Lawson showed that including a diabetes educator on the treatment team can enhance treatment adherence and glycemic control in patients with type 1 diabetes.<sup>24</sup>

### **Health system-related barriers**

One approach that has been demonstrated to help overcome both clinician- and health system-related barriers is to offer incentives to clinicians for achievement of better outcomes in their patients. This pay-for-performance approach has been shown to improve both screening and control of A1C levels.<sup>25</sup> Essential elements of such programs include specific guidelines and standards for clinicians, clearly defined performance metrics, and actionable feedback on performance.<sup>25</sup>

### **Patient-related barriers**

Overcoming patient-related barriers requires individualized patient management. Patients making lifestyle changes benefit from assistance in setting specific long-term goals as well as short-term behavioral targets. Goals and approaches to therapy should be tailored as much as possible to patient preferences. It may be necessary for treatment to progress in small steps in order to enhance the patient's confidence so that more intensive interventions may be initiated.

Coaching is a critical aspect of individualized therapy. PCCs should encourage positive choices and help patients overcome barriers to treatment success.<sup>26</sup>

Individualization of care must also consider a patient's race and ethnicity. The prevalence of diabetes is high in African Americans and Hispanic Americans, who also have poorer glycemic control than other groups.<sup>27</sup> Although these minority populations bear a high diabetes burden, we have been slow to develop culturally competent diabetes self-management programs for them.<sup>28</sup> Interventions for Spanish-speaking patients should also be improved. Such programs can achieve considerable success when properly designed and implemented. For example, results from a culturally tailored program for Mexican Americans<sup>29</sup> resulted in positive clinical and statistical effects on diabetes knowledge, weight, and body mass index. There were improvements in self-efficacy scores, as well as blood glucose and A1C levels, but these measures did not achieve statistical significance.

### Medication-related barriers

Barriers to treatment regimens can be lowered by choosing appropriate approaches to dose titration for both basal and bolus (also known as prandial) insulin. These regimens should be as simple as possible to increase the probability that they will be initiated by clinicians and adhered to by patients.<sup>30</sup> Simplicity can be achieved with once-daily basal insulin given in the morning or at night (at the same time each day), with the dose adjusted to maintain fasting plasma glucose (FPG) levels between 90 and 130 mg/dL.<sup>30</sup> Once FPG goals are attained, if the A1C is not controlled, bolus insulin therapy with a rapid-acting insulin analog to target postprandial glucose (PPG) is appropriate.<sup>30</sup> Several regimens for adjusting doses of basal and bolus insulin have been described in this supplement, but one that may be particularly useful is as follows: A head-to-head trial of the "2-4-6-8" titration scheme (dose adjusted weekly by FPG level) vs 2 units every 3 days found the latter to be superior. For simplicity, the authors recommend consideration of the approach of identifying an FPG goal, initiating 10 U of basal insulin, and instructing the patient to increase basal insulin 1 U daily until FPG is controlled (with the caveat to reduce insulin if FPG falls to <70 mg/dL).

Premixed insulin analogs may be used to intensify treatment in some patients. These preparations simplify treatment by permitting delivery of both basal and prandial insulin in a single injection at mealtimes. These formulations require fewer injections and less BG monitoring than premixed formulations that contained NPH and regular human insulin.<sup>31</sup> The use of insulin pens rather than a vial and syringe may also facilitate initiation of insulin therapy. These devices are generally favored by patients due to their ease of use and greater accuracy vs vials and syringes.<sup>32</sup> Results from one retrospective analysis of managed care claims data indicated that a switch from administration of insulin therapy by vial/syringe to a prefilled insulin analog pen device was associated with improved medication adherence, fewer claims for hypoglycemic events, reduced emergency department and physician visits, and lower annual treatment costs in patients with type 2 diabetes.<sup>33</sup>

Barriers related to regimen complexity can also be lowered by collaboration with diabetes educators. These specialists can help clinicians and patients become familiar with proven initiation and titration

protocols, and they can also provide printed titration schedules that will assist patients in managing their insulin regimens.<sup>3</sup>

### Characteristics of insulin

The characteristics of insulin that contribute to variable efficacy, high risk for hypoglycemia, and weight gain can all be reduced by substituting long- and rapid-acting insulin analogs for NPH and regular human insulin, respectively.<sup>34,20</sup> Insulin analogs can reduce regimen complexity by permitting once-daily administration of basal insulin and delivery of rapid-acting bolus insulin very shortly before or even after meals.<sup>35</sup>

### Hypoglycemia

The combination of long- and rapid-acting insulin analogs in basal-bolus therapy more closely mirrors physiologic insulin secretion than do human insulin products, and because insulin analogs are associated with less hypoglycemia than human insulin, this combination also helps to reduce the incidence and severity of hypoglycemic events.<sup>36,37</sup> Patient education has also been shown to significantly reduce the risk for hypoglycemia. For example, in a study by Nordfeldt et al,<sup>38</sup> there was a decline in the annual incidence of severe hypoglycemia from 42% to 25% in patients who received a videotape and brochure in which patients and medical experts reviewed in detail practical skills for glucose self-control and treatment aimed at preventing severe hypoglycemia. There was no change in the incidence of severe hypoglycemia for the control groups. Another strategy that may reduce patient concerns about hypoglycemic events is the use of patient medical alert bracelets and wallet cards. Making patients aware of the signs and causes of hypoglycemia can also help lower the barrier to effective insulin therapy.<sup>3</sup>

### Weight gain

The use of insulin analogs rather than human insulin may reduce weight gain.<sup>3</sup> A meta-analysis of clinical trials with insulin detemir has demonstrated that it is associated with less weight gain than is NPH insulin.<sup>39</sup> In contrast, a meta-analysis of clinical trial results indicated that insulin glargine does not consistently provide less weight gain than does NPH insulin in patients with diabetes.<sup>40</sup> Furthermore, results from a 52-week comparison of insulin detemir and insulin glargine as basal ther-

apy in 319 patients with type 2 diabetes indicated that mean weight gain at 52 weeks was significantly lower with detemir than with glargine (2.8 vs 3.8 kg,  $P < .05$ ).<sup>41</sup> Premixed insulin analogs also limit weight gain compared with human insulins. Boehm et al<sup>36</sup> found that patients with type 2 diabetes who were treated with insulin aspart 70/30 had significantly less weight gain compared with those treated with human premixed insulin.

Weight gain may result from patients increasing their carbohydrate intake to treat or prevent hypoglycemia or perceived hypoglycemia. The diabetes educator can assist in lowering this barrier to effective insulin treatment by reviewing the patient's blood glucose diary to determine (1) whether the patient is actually experiencing hypoglycemia, and (2) whether the patient is overeating to avoid hypoglycemic events, rather than matching carbohydrate intake to the severity of a reaction.<sup>3</sup>

### Optimizing adherence to insulin therapy in patients with type 2 diabetes

Interventions beyond those described in the preceding articles have been demonstrated to enhance

adherence to therapy and treatment efficacy in patients with diabetes. For example, a structured intensive diabetes education program can improve adherence to treatment as well as glycemic control and reduce the risk for hospitalization.<sup>42</sup> Web-based and cellular phone follow-up of patients taking insulin has been shown to result in a trend toward better glycemic control.<sup>43</sup> Intensive home-based psychological intervention has been shown to increase the frequency of blood glucose testing, improve metabolic control, and reduce inpatient admissions among patients with chronic poorly controlled diabetes. This intervention consisted of therapists meeting with families 2 to 3 times per week at the beginning of treatment. These sessions targeted adherence-related problems within the family, peer network, and community. Intervention techniques included cognitive-behavioral therapy, parent training, and behavioral family systems therapy.<sup>44</sup> Use of these approaches, as well as those described above, has the potential to ease the transition to insulin therapy and improve outcomes for patients with type 2 diabetes. ■

TEAR-OFF SHEET

## Helping your patient avoid and manage hypoglycemia

### Activities/habits that increase risk for hypoglycemia

- Failure to inject insulin at correct times (30 to 45 minutes prior to meals for short-acting regular insulin and 10 to 15 minutes before a meal for rapid-acting analogs and premixed insulin)
- More physical activity than usual
- Not eating on time
- Missing meals
- Drinking alcohol

### Signs of hypoglycemia

- Shakiness, lightheadedness
- Nervousness, irritability
- Confusion
- Hunger
- Tachycardia
- Sweatiness, feeling headachy
- Weakness
- Numbness or tingling in tongue or lips

### Guidance for managing hypoglycemia

- Self-treatment of minor hypoglycemia with consumption of fast-acting carbohydrates
- Glucagon injection kits for emergency treatment of major hypoglycemia (administered by family members)

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SUPPLEMENT TO

**THE JOURNAL OF**  
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## **PRACTICAL INSULIN STRATEGIES**

for type 2 diabetes  
in primary care

